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"Women and Cancer – Where Are We in Prevention, Early Detection and Treatment of Gynecologic Cancers?"

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INTRODUCTION

Mr. Chairman, Members of the Subcommittee, I am Richard Pazdur, M.D., Director of the Office of Oncology Drug Products, Office of New Drugs at the Center for Drug Evaluation and Research (CDER), Food and Drug Administration (FDA or the Agency). Prior to coming to FDA, I was associated with the M.D. Anderson Cancer Center in Houston, Texas, for 11 years, where I was involved in patient care, cancer research, medical education, and administration. Because of my prior experience with patient, academic and scientific communities, I am acutely aware of how FDA's decisions and requirements can impact the public we serve.

I particularly am pleased to be with you today, during Gynecologic Oncology Awareness Month and Ovarian Cancer Awareness Month, to discuss the topics of prevention, early detection and treatment of gynecologic cancers. My testimony will focus more on the treatment of these cancers since it is the Mission of FDA in this area to promote and protect the public health by assuring the safety, efficacy and security of human and veterinary drugs, biological products and medical devices by helping to speed innovations that make medicines more effective, safer and more affordable and to help the public obtain the accurate, science-based information they need to use these medicines to improve their health. I also will share with you what our Agency is doing to accelerate the delivery of innovative cancer treatments to meet the needs of cancer patients and their families. Further, I will discuss the Agency's interaction with other government agencies, drug sponsors and the medical professional community in an effort to streamline and accelerate the overall development of diagnostic, preventive and therapeutic interventions for cancer, as well as FDA's Critical Path Initiative. In my remarks, I will use the term "drug" to refer to both traditional small molecules and to therapeutic biological products.

RECENT CONSOLIDATION OF ONCOLOGY REVIEW FUNCTIONS AT FDA

Let me begin by informing you of recent structural changes within the Agency that are intended to provide a stronger and more consistent approach to the review process for drugs and most therapeutic biologics used to diagnose, treat and prevent cancer. In July 2004 FDA announced creation of a new Office of Oncology Drug Products (OODP or the Office) within CDER comprised of three previous areas within CDER responsible for the oversight of drugs and therapeutic biologics associated with cancer treatment and prevention. Three similar but new divisions within ODP were created entitled the Division of Drug Oncology Products, the Division of Biologic Oncology Products and the Division of Medical Imaging and Hematology Products. I am honored that this past April, I was selected as the first Director of OODP.

The Office also is to develop and lead a comprehensive Oncology Program to facilitate coordination of oncology activities across all Centers of FDA, and ensure ongoing outreach and collaboration between FDA, the National Cancer Institute (NCI) and other cancer-related organizations within and outside of the government. This cross cutting Oncology Program is to facilitate cross Agency expert consultation, provide a forum to discuss and develop regulatory policy and standards and serve as a focal point for Agency interaction and collaboration with oncology professional societies, NCI and other important stakeholders. The program also is to coordinate cross cutting training and oncology education programs.

The Office expects to improve the consistency of review and policy toward oncology drugs and bring together a critical mass of oncologists who will help guide the development of new therapies. Although many details of this new structure are still evolving, I am extremely pleased to be working with the many talented and dedicated scientists who comprise the Office, in order to realize FDA's vision for it.

CLINICAL TRIALS – The Phases of Clinical Trials

FDA's primary obligations are those vested in us by Congress in the Federal Food, Drug and Cosmetic (FD&C) Act and the Public Health Service (PHS) Act, that ensure that marketed medical products are safe, effective, and properly labeled and that experimental drug studies are designed to protect the patient volunteers. Before being approved by FDA for marketing, new drugs and biological products must be proven effective in controlled clinical trials and shown to be safe. In this context, safe is defined as a determination that the foreseeable risks are outweighed by the benefits of the new product under consideration. FDA is directed, under the FD&C Act, to rely on evidence of effectiveness based upon adequate and well-controlled studies. Those persons who participate in any trials under an Investigational New Drug (IND) application must be informed fully of the risks and possible benefits of their participation, and studies must be designed adequately to protect the patients from harm.

Most clinical trials are carried out in consecutive steps called phases. Each phase is designed to gather different types of information. Patients may be eligible to participate in studies in different phases, depending on their general condition, the type and stage of their cancer, and what therapy, if any, they already have had. Patients are seen regularly by the investigators during the study to determine the effect of the treatment, and treatment is stopped if side effects become too severe.

The purpose of a Phase 1 clinical trial is to find the best way to administer a new treatment and learn how much of it can be given safely. In a Phase 1 study, a new treatment is given to a small number of patients. For a new drug, the study starts by giving a low dose of the drug and, if necessary as preliminary findings of the trial suggest, the dose may then be adjusted as new patients enter the trial.

Phase 2 studies are designed to find out whether a treatment has the intended effect. In the context of cancer therapy, Phase 2 studies are designed to study whether the treatment actually damages cancer cells or slows their growth in people. Usually groups of 20 to 50 patients with one type of cancer receive an investigational treatment in Phase 2 studies. For example, patients with breast cancer who no longer respond to standard therapy may choose to be treated in a Phase 2 study. Patients are observed closely for anti-cancer effect by repeated measurement of tumor size to see whether tumors have shrunk since the beginning of the trial.

Phase 3 studies usually compare a new treatment that appeared to have an effect in the small Phase 2 studies with standard (generally accepted) therapy, or compare the combination of the new therapy and standard therapy to standard therapy alone. Phase 3 trials require larger numbers of patients; some trials enroll hundreds or even thousands of patients. Patients usually are randomized (assigned by chance) to the treatments being studied. The group that receives the standard

treatment is called the "control" group. The researchers expect that a certain number of these patients will be helped by the treatment. Phase 4 trials may be conducted after a drug has been approved. Companies often, for example, carry out studies of new drugs in patients with different tumors or with different stages of disease. FDA also may request, and the sponsor may agree to conduct, other post-marketing studies to provide additional data to improve the safe and effective use of the drug.

Clinical Trials for Cancer Therapy

The access process starts with a drug sponsor seeking to develop a new cancer drug, which is usually a pharmaceutical company or a research scientist at a university or at the National Cancer Institute (NCI) at the National Institutes of Health (NIH). Before clinical testing begins, researchers analyze the drug's main physical and chemical properties in the laboratory and study its pharmacologic and toxic effects in laboratory animals. These are known as pre-clinical studies. If the laboratory and animal study results show promise, the sponsor submits an IND application for FDA review prior to initiating testing in people.

In addition to FDA review of a protocol submitted to an IND the protocol also is subject to oversight by a local Institutional Review Board (IRB). An IRB is a panel of scientists and non-scientists that oversees clinical research, and approves the initiation of the protocol at their respective institution. Experienced clinical investigators give the drug to a small number of cancer patients who have no other available therapy. These phase 1 studies assess the most common acute adverse effects and examine the amount of drug that patients can take safely without unacceptable side effects. Initial clinical studies also begin to clarify what happens to a drug in the human body, how it is changed (metabolized), how much of it (or a metabolite) gets into the blood and various organs, how long it stays in the body, and how the body gets rid of the drug and its effects.

If Phase 1 studies do not reveal major problems, such as unacceptable toxicity, the next step is to conduct a clinical study in which the drug is given to patients who have medical conditions that may benefit from the potential cancer drugs. Several different types of cancers often are explored in these Phase 2 studies. Researchers then assess whether the drug has a favorable effect on the condition.

Testing experimental drugs in people inevitably presents ethical questions. A general principle, agreed on internationally, is that patients in a study must not be denied known effective treatment that prevents death or serious injury. In cancer trials, patients are never denied such treatment.

FDA recommends that anyone interested in participating in a clinical trial discuss the idea with his or her physician. Doctors may be able to provide information on investigational drugs that might be of benefit to their patients and of clinical trials involving these drugs. Patients can obtain detailed information from a variety of sources, including drug sponsors, FDA (if the information is public), and NIH. In fact, industry-sponsored trials are required statutorily to be listed on *www.clinicaltrials.gov*.

Clinical trials are carried out at major medical research centers, at NIH, and even in doctors' offices. Although they may involve hospitalized patients, many clinical trials can be conducted on an outpatient basis, with participants more or less going about their normal activities. The center or institution where a study is to be carried out may run newspaper advertisements recruiting potential participants for clinical studies that tell readers where to call or write for further information.

These aspects and other implications of taking part in a clinical trial must be explained fully in advance by the people conducting the trial, and patients must agree to the conditions before they can participate. The hope of personally benefiting from a new drug or the desire to take part in research that might one day benefit millions is what makes people volunteer for clinical trials. It should not prevent them, however, from finding out all they can about being a part of the process. They also must understand that new treatments, although promising, may prove ineffective or harmful.

EXPEDITING APPROVAL OF CANCER THERAPIES

The Food and Drug Administration Modernization Act (FDAMA), enacted November 21, 1997, amended the FD&C Act relating to the regulation of food, drugs, devices, and biological products. With the passage of FDAMA, Congress enhanced FDA's mission in ways that recognized that the Agency would be operating in a 21st century characterized by increasing technological, trade, and public health complexities. Among other things, FDAMA codified many of FDA's initiatives and existing programs designed to expedite drug development and expand access to unapproved therapies. All of these programs have been instrumental in shortening the time to marketing approval for cancer drugs and biologics.

FDA programs codified in FDAMA include:

- Expediting Approval of Cancer Drugs – FDA has shown a long-standing commitment to the prompt consideration and, when appropriate, early approval of new therapies for cancer patients. In 1996, the Agency launched its "Reinventing the Regulation of Cancer Drugs" initiative with the goal of accelerating the approval of and expanding patient access to cancer drugs. This program described how FDA's Accelerated Approval Rule or Subpart H Approval (21 CFR 314.510) and for biologics Subpart E (21 CFR 601.40) would be used to approve cancer drugs earlier in their development and for expanded access programs (the treatment IND) to be used to make promising drugs broadly available prior to marketing.

    - Accelerated Approval or Subpart H or Subpart E Approval - Under the Accelerated Approval Rule subsequently incorporated into the Fast Track provision of FDAMA (section 112), FDA can approve treatments for serious or life-threatening conditions that demonstrate the potential to address unmet medical needs on the basis of a "surrogate endpoint" that is "reasonably likely" to predict clinical benefit. A surrogate endpoint is a measure of drug effect (e.g., tumor shrinkage) that does not by itself show a patient benefit, such as decreased pain or longer survival, but is thought likely to lead to such a benefit. Some surrogate endpoints are well established (blood pressure, for example) and

are a routine basis for approval. Other surrogate endpoints are not as certain, and these may now be used under our Accelerated Approval authority. The reinvention program specifically declared that FDA would rely on tumor shrinkage in refractory cancer as a basis for approval, and we have done so regularly. Since 1996, four out of nine biological products were approved under accelerated approval, and many new drug approvals have been based on this study endpoint, allowing for earlier marketing than would have been possible had FDA waited for a documented effect on such an endpoint or survival. Under accelerated approval, the manufacturer commits to study the drug's actual clinical benefit after marketing.

- Priority Review-When marketing applications are submitted they are designated as priority (P) or standard (S). Priority New Drug Applications (NDAs) and effectiveness supplements are those that could have important therapeutic impacts. A priority designation is intended to direct overall attention and resources to the evaluation of applications for products that are reported to have the potential for providing significant therapeutic advances. Specifically, FDA's goal is to review a priority within 6 months rather than the standard review time of 10 months. Since 1996, 13 biologics (9 Biologic License Applications (BLA) and 4 supplements) and 55 drugs (27 NDAs and 28 supplements) for cancer therapies have received priority review and approval.

- Fast Track refers to a process for frequent and timely interaction with FDA during drug development. The fast track programs are designed to facilitate the development of and expedite the review of new drugs and biologics to treat serious or life-threatening conditions that demonstrate the potential to address unmet medical needs. To provide clear information to industry regarding participation in the fast track process, FDA issued a guidance document on this provision in September 1998.

Fast-track designation for a clinical development program can occur at any time of the development process. It is initiated by the sponsor's request for designation and can be granted for any development program (as projected by the sponsor) that is intended to demonstrate that its drug/biologic will affect a serious or life-threatening disease or condition. This may be an improvement over existing therapy or treatment where no alternative therapy exists.

Recently two exploratory pilot programs were instituted to build on the current practice of interaction between FDA and applicants during drug development and application review.

- *Pilot 1, Reviewable Units for Fast Track Products*, provides for the review of a limited number of presubmitted portions of an applicant's marketing application (reviewable units) based on the terms and conditions agreed upon by the applicant and FDA.
- *Pilot 2, Scientific Feedback and Interactions During Development of Fast Track Products*, provides frequent feedback based on a prospectively defined agreement between FDA and applicants.

It is important to note that FDAMA did not alter FDA's effectiveness standard, except by giving explicit authority to the Agency to rely on data from a single, adequate and well-controlled clinical investigation and confirmatory evidence as support for approval in certain cases. Even for drugs intended for serious and fatal illnesses, there must be substantial evidence that the drug

will have the effect it purports to have. As noted, however, the law recognizes that the nature of the effect that needs to be demonstrated might vary depending on the urgency and clinical need.

PLANNED WORKSHOP ON OVARIAN ENDPOINTS

We currently are in the early stages of planning a workshop to discuss endpoints related to ovarian cancer and hope to hold this meeting sometime in early 2006. Planning for workshops is guided by a steering committee that includes representation from FDA, NCI, the American Society of Clinical Oncology, and the American Association for Cancer Research. Workshop participants will include oncology experts, radiation oncologists, statisticians, industry representatives, and patient advocates.

In late 2002, FDA embarked on a project to evaluate potential endpoints for cancer drug approval. Endpoints have been examined for the most common cancers: lung, colon, and prostate cancer. For each cancer, FDA held public workshops to identify important issues, and these issues were later discussed in meetings of the Oncologic Drugs Advisory Committee (ODAC). Subsequently, guidance documents will be published describing FDA's current thinking on endpoints for cancer drug approval. In June 2005, FDA co-sponsored a workshop with the American Society of Hematologists (ASH) to explore endpoints in acute leukemias.

EXPANDED ACCESS TO INVESTIGATIONAL NEW DRUG PRODUCTS

Also codified in FDAMA are the procedures known as a Single Patient IND or Treatment IND. FDA believes it is appropriate to make certain promising, but not yet approved, products available to patients with serious and life-threatening illnesses who lack alternative treatment. A major goal of the treatment IND proposed in 1982, and made final in 1987, was to make unapproved but promising drugs with appropriate evidence of effectiveness widely available prior to marketing. In the past such drugs often were available but only at selected sites. There also is a process for giving expanded access to unapproved medical devices. Exactly what to do and the Agency's role in the process are described in the oncology part of FDA's website*:* *www.fda.gov/cder/cancer/singleIND.html*.

LIST OF DRUGS APPROVED FOR TREATMENT OF OVARIAN CANCER

A list of the drugs approved for the treatment of gynecologic cancers is at the end of this testimony at Attachment A. New therapies for the treatment of gynecologic cancer is an area of active clinical investigations. Publicly available information on active clinical trials is available at *www.clinicaltrials.gov*. Hundreds of clinical trials in ovarian, cervical, endometrial and other gynecologic cancers are listed.

FDA OFFICE OF SPECIAL HEALTH ISSUES

FDA staff is aware of the concerns that patients with life-threatening illnesses and their families experience when trying to obtain information about potentially helpful therapies, especially when there is no treatment for their disease. In addition to staff within FDA's medical product centers that routinely provide assistance and information to consumers, FDA, in 1988, created the Office

of Special Health Issues (OSHI), with trained staff to work with patients with life-threatening diseases. The skilled staff of OSHI works with patients who have serious or life-threatening diseases such as AIDS, cancer, Parkinson's disease, or Alzheimers disease, to name a few.

Patients usually call to obtain information about unapproved treatments currently being researched. Once our staff explains that FDA cannot disclose certain confidential information about drugs or devices that are not yet approved, we direct callers to listings of clinical trials where they can locate a trial for which they might be eligible.

We are able to talk with patients about any treatment that appears in a public access database, such as the *ClinicalTrials.gov* database operated by the National Library of Medicine or NCI's database at *http://cancertrials.nci.nih.gov*. Our staff is working actively with the National Library of Medicine and the pharmaceutical industry to include more clinical trials in the *ClinicalTrials.gov* database. If a patient does not have a computer, a patient can access the NCI's clinical trials listing by calling 1-800-4-CANCER. An information specialist will search the database and send the trials information to the patient within 3 days.

Our goals in serving patients with life-threatening diseases and their family members are straightforward:

- Promptness (returning patients' and family members' calls within 24 hours);
- Accessibility (listening to the caller's concerns and giving the caller as much time as he or she needs);
- Education (about the drug approval process and his or her options); and
- Assistance (providing additional information to the patient or family member that may be helpful, e.g. other sources of information).

FDA/SPONSOR INTERACTION DURING CLINICAL TRIALS AND THE DRUG REVIEW PROCESS

FDA receives reports about on-going clinical studies to ensure that subjects who volunteer for studies are protected and that the quality and integrity of scientific data are maintained. FDA makes itself available to interact with product sponsors during the drug review process as indicated in the diagram at Attachment B, showing the Drug Development Pipeline. Formal meetings were established by Congress under the FDA Modernization Act of 1997, and FDA has committed to performance goals for such meetings under the Prescription Drug User Fee program. These meetings can occur from the pre-IND phase all the way to pre-NDA/BLA submission. FDA receives requests for and convenes over 2,000 such meetings with sponsors each year which can help sponsors clarify research questions that need to be addressed, identify earlier the unsuccessful compounds, and focus research on studies of compounds that are more likely to lead to approval.

THE NCI/FDA INTERAGENCY ONCOLOGY TASK FORCE (IOTF)

The Interagency Oncology Task Force (IOTF) was formed early in 2003 by Dr. Andrew von Eschenbach, Director of the National Cancer Institute, and Dr. Mark McClellan, then Commissioner of Food and Drugs. The formation of the IOTF was an important strategic step toward achieving FDA's goal of increasing the availability and use of safe and effective treatments for cancer, and NCI's challenge goal of eliminating suffering and death from cancer by 2015. The purpose of the IOTF is to leverage the expertise and capabilities of both agencies for the expressed purpose of streamlining and accelerating the overall development of diagnostic, preventive and therapeutic interventions for cancer.

Since its formation, the members of IOTF collaboratively have undertaken an analysis of the overall development and review process for new oncology drugs and devices and identified several specific initiatives that are directed toward optimizing drug and device development. NCI is working to specifically gather and synthesize the scientific support needed by FDA to address specific regulatory issues. FDA is working cooperatively with NCI to address important scientific issues including:

- Committing to encourage physicians and scientists to become expert in clinical research, the clinical approval process and the translation of laboratory science into new products for cancer through high quality training,

- Developing markers of clinical benefit using imaging in oncology drug development, collaborative development of the scientific data needed to establish improved surrogate endpoints for cancer clinical trials, and the potential utilization of advanced technologies,

- Utilizing bio-informatics technology to expand the use of an electronic form of the IND application,

- Establish a process to facilitate the interaction between NCI-supported investigators and FDA during any phase of the regulatory review process,

- Enhancing scientifically driven review of the pre-clinical requirements for IND filings; and

- Developing the scientific base for consistent review of cancer prevention agents.

The IOTF is meeting regularly and actively addressing issues that can ultimately speed the development of new advanced interventions for cancer. The IOTF subcommittees are currently developing resource materials that will assist investigators in preparing the data needed for FDA's regulatory process. FDA has already responded with guidance documents (such as a recent guidance on pharmacogenomics) and process changes.

FDA's CRITICAL PATH INITIATIVE

On March 16, 2004, FDA issued a report entitled, "Advancing America's Health; Advancing Medical Breakthroughs." This "Critical Path" paper calls for academic researchers, product developers, and patient groups to work with FDA to help identify opportunities to modernize tools for speeding approvable and innovative products to market to improve public health. The report provides FDA's analysis of the current pipeline problem -- the recent slowdown, instead of the expected acceleration, in innovative medical therapies reaching patients, and suggestions for addressing this problem.

Today's revolution in biomedical science has raised new hope for the prevention, treatment, and cure of serious illnesses. However, there is growing concern that many of the new basic science discoveries made in recent years may not yield quickly more effective, affordable, and safe medical products for patients. This is because the current medical product development path is becoming increasingly challenging, inefficient, and costly. During the last several years, the number of new drug and biologic applications submitted to FDA has declined significantly; the number of innovative medical device applications also has decreased. In contrast, the costs of product development have soared over the last decade. Because of rising costs, innovators often concentrate their efforts on products with potentially high market return. Emerging contenders for resources include the development of products targeted for important public health needs (e.g., counter terrorism), less common diseases, prevalent third world diseases, prevention indications, or individualized therapy is becoming increasingly challenging. In fact, with rising health care costs, there now is concern about how the nation can continue to pay even for existing therapies. If the costs and difficulties of medical product development continue to grow, innovation will continue to stagnate or decline and the biomedical revolution may not deliver on its promise of better health. Attachment C to this testimony demonstrates this for drugs and biologics through 2002.

A problem, in FDA's view, is that the applied sciences needed for medical product development have not kept pace with the tremendous advances in the basic sciences. The new science is not being used to guide the technology development process in the same way that it is accelerating the technology discovery process. For medical technology, performance is measured in terms of product safety and effectiveness. Not enough applied scientific work has been done to create new tools to get fundamentally better answers about how the safety and effectiveness of new products can be demonstrated, in faster time frames, with more certainty, and at lower costs. In many cases, developers have no choice but to use the tools and concepts of the last century to assess this century's treatment candidates. As a result, the vast majority of investigational products that enter clinical trials fail. Often, product development programs must be abandoned after extensive investment of time and resources. This high failure rate drives up costs, and developers are forced to use the profits from a decreasing number of successful products to subsidize a growing number of expensive failures. Finally, the path to market, even for successful candidates, is long, costly, and inefficient, due in large part to the current reliance on suboptimal assessment methods.

A new product development toolkit -- containing powerful new scientific and technical methods such as animal or computer-based predictive models, biomarkers for safety and effectiveness, and new clinical evaluation techniques -- is needed urgently to improve predictability and

efficiency along the critical path from laboratory concept to commercial product. Superior product development science is needed to address these challenges -- to ensure that basic discoveries turn into new and better medical treatments. More efforts need to be directed at creating better tools for developing medical technologies. Finally, we need a knowledge base built not just on ideas from biomedical research, but also on reliable insights into the pathway to patients.

FDA is planning and beginning an initiative that will identify and prioritize (1) the most pressing development problems and (2) the areas that provide the greatest opportunities for rapid improvement and public health benefits. This will be done for all three dimensions along the critical path -- safety assessment, evaluation of medical utility, and product industrialization. It is critical that we enlist all relevant stakeholders in this effort. We are in the final stages of developing a Critical Path Opportunity List, based on the input and ideas contributed both by external stakeholders and FDA reviewers. Concurrently, FDA has refocused its internal efforts to ensure that we are working on the most important problems and intensified our support of key projects. We are working closely with NCI under the IOTF on proposals to advance the science of cancer drug development.

Through scientific research focused on these challenges, we can improve the process for getting new and better treatments to patients. Directing research not only to new medical breakthroughs, but also to breakthrough tools for developing new treatments, is an essential step in providing patients with more timely, affordable, and predictable access to new therapies. We are confident that, with effective collaboration between government, academia, and the private sector, these goals can be achieved.

CONCLUSION

FDA is working with NCI, industry, academia, patient and other organizations to ensure that cancer patients receive safe and effective drugs. FDA also is working hard to improve patient access to promising cancer treatments without compromising patient safety. Furthermore, we are working to ensure that patients have timely and important information about available cancer drugs including those for gynecologic cancer indications. Our goal is to improve upon a system that supports all cancer patients, and all other patients seeking access to new drugs and treatments for their disease.

Thank you for this opportunity to testify. I will be happy to answer any questions the Subcommittee might have.